REMARKS

Specification and Claims

Applicants filed on February 11, 2002 a new application including the following documents:

Specification of 11 pages;
6 sheets of figures that included Fig (1) set forth on 4 pages and additional figures 1.1-1.4 on the last two pages;
a preliminary amendment that amended claims that were filed in an Article 34 submission during the prosecution of the corresponding PCT application; and
a signed declaration was filed on July 29, 2002.

Applicants filed a Sequence Listing, CRF and Statement of Identity on June 20, 2002 and than again on February 28, 2003. Applicants include herewith a replacement Statement of Identity that meets all requirements under 1.821(g).

Further, applicants have reviewed pending claims and the specification and have made any necessary corrections regarding SEQ ID numbers.

Claim Objections

Claims 9 and 17 were objected to because of improper form. Applicants have amended the claims thereby obviating this objection.

Claims 3, 4, 6, 14-16 and 18 were objected to because according to the Office these claims expand rather than limit the scope of claim 1. The Office suggests that mutations T363A, T394A and T463A are excluded from Claim 1. Applicants disagree and request that the Office review this matter in light of the following discussion.

Initially it should be noted that different tests discussed in the specification are described in Table 1, set forth at page 10 of the specification, which compiles the results of the

different testing methods for the variants. These testing methods are well-known and available to one skilled in the art. For example, the notation "P38-TA" refers to a testing method to show transactivation acitivity of the P38 promoter; "ACCA" indicates binding tests of the NS1 specifically to $[ACCA]_{2-3}$ motifs that are present at multiple sites on the viral genome; "Nick 1, 2 and 3" are NS1 mediated site-specific nicking and the consequent covalent attachment of the NS1 to the 5' end of the nicked product, the different nicking tests were conducted under different conditions; "Heli" represents the results of a Helicase assaying; "Rep" indicates testing results relating to the replication ability of the NS1 to trigger viral replication from a NS deleted molecular clone; and "Cyto" describes the results of the toxicities of the different variants which involves the ability of the variants to inhibit stable DNA transformation of cells after cotransfection with NS-protein producing and selectable plasmids. All of these tests are known to one skilled in the art and can be found in the reference cited in the specification at page 3, in the last paragraph.

New claim 21 recites;

> 21. A parvovirus NS 1 variant protein having a shifted equilibrium between the DNA replication and transcription activities (a), and the cytotoxicity activity (b), wherein the parvovirus NS 1 variant protein comprises a mutated phosphorylation site and wherein the shifted equilibrium is selected from the group consisting of:
>
> (1) DNA replication activity is reduced, transcription activity is eliminated and cytotoxicity is maintained or increased; and
>
> (2) DNA replication activity and transcription activity is maintained or increased and cytotoxicity is reduced or eliminated.

Thus (a) relates to DNA replication and transcription activities; and

(b) relates to cytotoxicity activities.

According to the Office, the mutations T363A, T394A and T463A are excluded from Claim 1, because the Office mistakenly believes they do not exhibit the requirements of claim 1, as previously written. Applicants disagree and refer to the results shown in Table 1 in light of the description of the different testing methods as set forth above.

Variant **T363A** showed a reduction in (b) cyto activity and also showed an increase in binding tests to $[ACCA]_{2-3}$ motifs that are present at multiple sites on the viral genome relative to the wild type, and as such, transcription acitivity is increased and fits within the criteria of option **(2).**

Variant **T394A** maintained cyto activity and showed a reduced replication and transactivation activity relative to the wild-type, and as such fits within the criteria of option **(1).**

Variant **T463A** showed a reduction in cyto activity and maintained activity in replication and transactivation activity relative to the wild-type, and as such fits within the criteria of option **(2).**

For completeness, variant **S283A** shows a marked increase in cyto activity and a reduction in replication and transactivation activity relative to the wild-type, and as such fits within the criteria of option **(1)** and newly added claim 21.

As such, it is evident that all the mutations are included within the scope of previously presented claim 1.

Rejections of Claims and Traversal Thereof

In the May 27, 2004 Office Action,

claims 1-8, 10-16, and 18 were rejected under 35 U.S.C. §112, second paragraph;

claims 1-8, 10-16 and 18 were rejected under 35 U.S.C. §112, first paragraph;

claims 8, 12 and 13 were rejected under 35 U.S.C. §101;

claims 1-3, 5-8, 11, 14 and 16 were rejected under 35 U.S.C. §102(b) as being anticipated by Legender, et al., (*Journal of Virology* 66: 5705-5713, 1992);

claims 10 and 18 were rejected under 35 U.S.C. §102(b) as being anticipated by Yeung, et al., (*Virology* 181: 35-45 1991); and

claims 1, 2, 5, 10, 11, 14 and 16 were rejected under 35 U.S.C. §102(b) as being anticipated by or in the alternative, under 35 U.S.C. §103(a) as obvious over Moffatt, et al. (*Journal of Virology* 72: 3018-3028 1998).

These rejections are hereby traversed, and reconsideration of the patentability of amended claims herein is requested, in light of the ensuing remarks.

Rejection under 35 U.S.C. §112, second paragraph

Claims 1-8, 10-16, and 18 were rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have amended the claims thereby obviating this rejection. Accordingly, applicants request the withdrawal of this rejection under U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §112, first paragraph

Claims 1-8, 10-16 and 18 were rejected under 35 U.S.C. §112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The Office states that the NS1 variants S283A, T363A, T394A and T463A, are enabling.

The Office asserts that the specification does not reasonably provide enablement for "a shifted equilibrium between the DNA replication and transcription activities (a) and the cytotoxicity activity (b), or even for the Markush group recited in claim 1. Applicants disagree, however to move prosecution forward have amended claim 1, thereby obviating this rejection.

According to the Office, claims 12 and 13 involve "treating tumoral disease" and "gene therapy," and the "specification provides no working examples of these uses." Applicants submit that Example 4 discusses the use of expression vectors containing the NS1 variants according to the present claims that were packaged either in vivo or in vitro and packaged transducing particles were isolated. These transducing units containing the NS1 variants were used not only for studies concerning gene regulation in tissue culture and animals, but also as therapeutic agents either alone or in combination with other agents (such as cytokines) in gene and cancer therapy approaches.

Based on the foregoing arguments and the amendments presented herein, applicants have overcome all 35 U.S.C. §112 rejections and request that the Office withdraw such rejections.

Rejection under 35 U.S.C. §101

Claims 8, 12 and 13 were rejected under 35 U.S.C. §101 because the claimed invention is directed to non-statutory subject matter. Applicants have amended the claims thereby obviating this rejection. Applicants request that this rejection be withdrawn.

Rejection under 35 U.S.C. §102(b)

Claims 1-3, 5-8, 11, 14 and 16 were rejected under 35 U.S.C. §102(b) as being anticipated by Legender, et al. Applicants submit that the Legender, et al. reference does anticipate the presently claimed invention.

According to the Office:

> "The NS1 mutant pULB3201 has DNA replication activity reduced (to undetectable), p38 transactivation eliminated, and cytotoxic activity maintained. This deletion mutant includes the sites recited in claims 3 and 14. Therefore the publication meets each and every limitation of these claims."

Applicants disagree and submit that the variant pULB3201 does not exhibit "maintained" cytotoxic activity. As a matter of fact, as shown in Table 1, at page 5709, column 2, it is evident that the NS1 mutant pULB3201 showed a decrease in cytotoxic effects. The

pMM984Δ plasmid, considered the wild type showed very high cytotoxic activity (2 colonies survived) while the pULB3201 plasmid showed a reduction in the cytotoxicity activity because 29 colonies survived. Thus, the cytotoxic activity was not maintained.

As such, the NS1 mutant pULB3201 plasmid does not disclose, teach or suggest each and every element of applicants' claimed invention. Applicants respectfully request the withdrawal of this rejection under 35 U.S.C. §102(b).

Claims 10 and 18 were rejected under 35 U.S.C. §102(b) as being anticipated by Yeung, et al. Applicants submit that Yeung, et al. does not anticipate applicants claimed invention.

To anticipate a claim or render it obvious, a reference must be enabling. This point was recently reaffirmed in an April 7, 2000 decision of the Court of Appeals for the Federal Circuit (CAFC).[1] Citing *In re Paulsen*,[2] the court stated that to be anticipating, a prior art reference must:

1) disclose each and every limitation of the claimed invention;

2) be enabling; and

3) describe the claimed invention sufficiently to place it in possession of a person of ordinary skill in the field of the invention.

Yeung, et al. does not meet this standard.

Applicants' claim 10 recites:

10. An antibody, directed against the parvovirus NS 1 variant protein according to claim 1.

Claim 1 defines specific mutated variants including the parvovirus NS 1 variants comprising mutations S283A (SEQ ID NO. 6); T363A (SEQ ID NO. 10); T394A (SEQ ID NO. 14) or T463A (SEQ ID NO. 18). Each one of these mutants has very different

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[1] *Helifix Ltd. v. Blok-Lok, Ltd.*, 54 USPQ2d 1299 (Fed. Cir. 2000).
[2] *In re Paulsen*, 31 U.S.P.Q.2d 1671, 1673 (Fed. Cir. 1994).

activities relating to replication, transactivation and cytotoxicity, relative to a wild-type parvovirus NS 1 protein. Thus, the differences between these mutants clearly indicate a difference in the tertiary structure due to the mutations.

The Yeung, et al. reference discusses the formation of six different Mab raised against a fusion protein that contains amino acids 364 to 623 of the NS-1 of MVMp. It is true that these six Mab recognize the 83-kDa protein, likely the wild-type NS-1 in infected mouse fibroblast cells, but there is no disclosure, teaching or suggestion that these antibodies can or will recognize the mutants of applicants' claimed invention. As stated above, each one of these mutants exhibit entirely different activities from the wild NS-1 protein and as such there is no indication that any of these Yeung, et al antibodies would recognize or have any affinity for the mutant variants of the presently claimed invention.

While the Office speculates that these antibodies would inherently recognize the mutant variant of the present invention, it is the Office's burden to provide evidentiary support of this statement because the reference certainly does not provide such support.

As stated above, a reference is not anticipating unless it discloses each and every limitation of the claimed invention; it is enabling; and it describes the claimed invention sufficiently to place it in possession of a person of ordinary skill in the field of the invention. The Office has not provided any evidence on how a person of ordinary skill in the art would read the cited reference and determine the exact mutation such as that described in applicants' claimed invention without an undue amount of experimentation. *See In re Sheppard* , 144 USPQ 42, (CCPA 1981) (reversing a rejection under 35 U.S.C. Section 102(b) where the asserted prior art reference did not permit someone skilled in the art to possess the claimed invention). Clearly, the cited reference is not enabling and does not put the claimed invention in the hands of one skilled in the art. (*In re Sun*, 31 USPQ2d 1451 (Fed. Cir. 1993)). Specifically, in the publication by Yeung, et al, some of the antibodies bind to an epitope while others do not, and as such, there is no disclosure or even expectation that these Mabs would bind to applicants' claimed mutant variants.

Additionally, the Yeung, et al. reference does not identically disclose or describe

applicants' claimed invention. Initially, none of the fusion proteins used to generate the Yeung, et al antibodies are the same as that of applicants' claimed mutant variants. Thus, the Yeung, et al. reference has not "identically disclosed or described" the presently claimed invention as required of an anticipatory reference applied under section 102. (See *In re Felton*, 179 USPQ 295 (CCPA 1973)).

Further, the antibodies of applicants' claimed invention are not expressly or inherently described in Yeung, et al. It is well settled as a matter of law, that inherency cannot be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency. *In re Oelrich*, 212 USPQ 323 (CCPA 1981). Instead, it must consistently occur each and every time, which is necessary under case law to prove inherency. Thus, the Mabs of Yeung, et al. would have to recognize applicants' claimed mutant variants each and every time and there is nothing in the Yeung, et al. reference that would indicate such an occurrence especially in light of the diversity and specificity shown by the Mabs of Yeung, et al.

Accordingly, applicants respectfully submit that claim 10 is patentably distinguishable over Yeung, et al. Withdrawal of this rejection under 35 U.S.C. §102(b) is requested.

Rejection under 35 U.S.C. §102(b)/103(a)

Claims 1, 2, 5, 10, 11, 14 and 16 were rejected under 35 U.S.C. §102(b) as being anticipated by or in the alternative, under 35 U.S.C. §103(a) as obvious over Moffatt, et al. Applicants submit that Moffatt, et al., does not anticipate or render obvious applicants' claimed invention.

Moffatt, et al. describes disruption of the nucleoside triphosphate (NTP) binding domain on NS-1 by designing point mutations at amino acid residue 334 and 332. These mutants suppressed the cytotoxic activity of NS-1, albeit not completely as discussed at page 3022, column 2. The authors determined that these NTP-1 binding domains were essential for the induction of apoptosis and cell cycle arrest.

According to the Office;

> "One of these mutations changes a threonine residue, which reasonably appears to be a phosphorylation site (since three of the four sites disclosed by the instant specification involve mutation of a threonine reside).

Thus, the Office is speculating that because a threonine residue is located on nucleoside triphosphate (NTP) binding domain that this must also be an area deemed to be a phosphorylation site. Applicants disagree and suggest that mere speculation is not sufficient for the Office to meets its burden of establishing a *prima facie* case of obviousness. Firstly, it is well known that phosphorylation sites are not usually located at the same general location as that of a NTP binding site. Instead, phosphorylation sites are usually considered to be involved in the nucleotide hydrolysis, and as such, are located either upstream or downstream from the NTP binding site. Clearly, the placement of a threonine residue does not teach or suggest that this NTP binding site is also a phosphorylation site, especially to one skilled in the art that would likely doubt such an occurrence.

Contrary to the Office's contention, there is no suggestion in the reference to alter the mutation of the NTP binding domain to that of a phosphorylation site. Thus, the Office seems to be merely reinterpreting the prior art in light of applicants' disclosure, in order to reconstruct applicants' claimed invention, but without any instructional or motivating basis in the references themselves. Such approach is improper and legally insufficient to establish any *prima facie* case of obviousness.

Further, obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert,* 28 USPQ2d 1955 (Fed. Cir. 1993). A mutation at a phosphorylation site was not known in the cited reference. Therefore, how could a skilled artisan make any modification while arriving at an invention that possesses the heretofore unknown mutation. While it is possible that, serendipitously, the invention would have such a feature, serendipity is not a valid basis for asserting obviousness.

The Office further contends that Moffatt teaches an antibody reactive with the NS1 protein. However, there is no disclosure, teaching or suggestion that these antibodies

can or will recognize the mutants of applicants' claimed invention. As stated above, clearly each one of these mutants exhibit entirely different activities from the wild NS-1 protein and as such, there is no indication that the Moffatt antibody would recognize or have any affinity for the mutant variants of the presently claimed invention.

In light of the above discussion, applicants respectfully request that the rejection of claims 1, 2, 5, 10, 11, 14 and 16, on the basis of lack of novelty or obviousness, be withdrawn.

Fees Payable and Petition for Extension of Time

Applicants hereby petition for a one-month extension of time, extending the deadline for responding to the May 27, 2004 Office Action from August 27, 2004 to September 27, 2004. The entry of this petition results in a petition fee of $55.00.

Two new independent claims are added beyond the number for which a fee has previously been paid, resulting in an added claims fee of $86.00. Applicants canceled eight dependent claims herein.

A credit card form in the amount of $141.00 is submitted herewith in payment of the petition fee and added claims fees. The U.S. Patent and Trademark Office is hereby authorized to charge any additional amount necessary to the entry of this amendment, and to credit any excess payment, to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

Conclusion

Applicant has satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Mosher reconsider the patentability of claims 1, 5-13 and 19-21 in light of the distinguishing remarks herein, and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Mosher is requested to contact the undersigned attorney at (919) 419-9350 to resolve same.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent Application of:		**Docket No.:**	**4121-136**
Applicant:	**Nuesch, et al.**	**Confirmation No.:**	**9054**
Application No.:	**10/069,056**	**Examiner:**	**Mary Mosher**
Date Filed:	**February 11, 2002**	**Group Art Unit:**	**1648**
Title:	**PARVOVIRUS NS 1 VARIANTS**	**Customer No.:**	**23448**

STATEMENT OF IDENTITY UNDER 37 C.F.R. §1.821 (f) AND (g)

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I hereby state that I prepared the paper copy of the document titled "Sequence Listing_resubmit.ST25" and recorded such document on computer readable form on February 27, 2003, and that information recorded in computer readable form was identical to that on the paper copy of sequence listing submitted.

I hereby further state that the sequence Listing submitted on February 27, 2003 did not introduce any new matter in the present application.

Respectfully submitted,

Marianne Fuierer 9/27/04

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